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=> s neurotroph?(l)pyrrolidin?
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=> s l1 and py<1998
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L2            4 L1 AND PY<1998

=> d bib hit 1-4

L2   ANSWER 1 OF 4  CAPLUS  COPYRIGHT 2006 ACS on STN
AN   2002:332684  CAPLUS
DN   136:340999
TI   Preparation of amino acid derivatives as rotamase enzyme activity
     inhibitors
IN   Steiner, Joseph P.; Hamilton, Gregory S.
PA   USA
SO   U.S. Pat. Appl. Publ., 40 pp., Cont.-in-part of U.S. Ser. No. 359,351.
     CODEN: USXXCO
DT   Patent
LA   English
FAN.CNT 8
     PATENT NO.          KIND   DATE        APPLICATION NO.         DATE
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PI   US 2002052410        A1    20020502    US 2001-805249          20010314
     US 5614547           A     19970325    US 1995-479436          19950607 <--
     US 2002013344        A1    20020131    US 1995-551026          19951031
     RU 2269514           C2    20060210    RU 2000-115383          19960605
     US 6509477           B1    20030121    US 1999-359351          19990721
PRAI US 1995-479436       A1    19950607
     US 1995-551026       A2    19951031
     US 1996-693003       B1    19960806
     US 1999-359351       A2    19990721
     RU 1997-111860       A3    19960605
OS   MARPAT 136:340999
     PATENT NO.          KIND   DATE        APPLICATION NO.         DATE
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PI   US 2002052410        A1    20020502    US 2001-805249          20010314
     US 5614547           A     19970325    US 1995-479436          19950607 <--
     US 2002013344        A1    20020131    US 1995-551026          19951031
     RU 2269514           C2    20060210    RU 2000-115383          19960605
     US 6509477           B1    20030121    US 1999-359351          19990721
AB   The invention relates to methods of using neurotrophic compds.
     having an affinity for FKBP-type immunophilins to stimulate or promote
     neuronal growth or regeneration and to prevent neuronal degeneration.
     Amino acid derivs. R1C(:X)CON(J)CHKCO-Y(CH2)nCHZR2 [n = 0-3; Y is CH2, O,
     NH, or alkylimino; Z and R2 are independently Ar, or cycloalkyl,
     cycloalkenyl, or Ar-(un)substituted alkyl or alkenyl, or TCH:C(Q)CH2-,
     where Q = H, alkyl or alkenyl; T is Ar or substituted cycloalkyl; Ar is an
     (un)substituted mono or bicyclic heterocyclic aromatic ring; R1 is U, where U
     is H, (un)substituted alkyl, alkoxy, alkenyl, alkenyloxy, cycloalkyl or
     cycloalkenyl; X is O or CH-U , provided that if R1 is H, then X is CH-U or
     if X is O then R1 is U; J is H, alkyl or benzyl; K is alkyl, benzyl or
     cyclohexylethyl; or J and K may be taken together to form a 5-7 membered
     heterocyclic ring which may contain O, S, SO or SO2] or their
     pharmaceutically acceptable salts are claimed.  Thus, 3-(3,4,5-
     trimethoxyphenyl)propyl (2S)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-
     pyrrolidinecarboxylate was prepared by esterification of the acid
     and showed Ki = 0.025 μM for inhibition of rotamase and ED50 = 80 nM
     for neurite outgrowth in chick dorsal root ganglion (DRG) cultures.

L2   ANSWER 2 OF 4  CAPLUS  COPYRIGHT 2006 ACS on STN
```

AN 2002:276521 CAPLUS
DN 136:310178
TI Preparation of amino acid derivatives as rotamase enzyme activity inhibitors
IN Steiner, Joseph P.; Hamilton, Gregory S.
PA USA
SO U.S. Pat. Appl. Publ., 39 pp., Cont.-in-part of U.S. Ser. No. 551,026.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 8

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI	US 2002042377	A1	20020411	US 2001-873298	20010605	
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PRAI	US 1995-479436	A1	19950607			
	US 1995-551026	A2	19951031			
	US 1996-693003	B1	19960806			
	US 1999-359351	A2	19990721			
	RU 1997-111860	A3	19960605			

OS MARPAT 136:310178

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	RU 2269514	C2	20060210	RU 2000-115383	19960605	
	US 6509477	B1	20030121	US 1999-359351	19990721	

AB The invention relates to methods of using **neurotrophic** compds. having an affinity for FKBP-type immunophilins to stimulate or promote neuronal growth or regeneration and to prevent neuronal degeneration. Amino acid derivs. R1C(:X)CON(J)CHKCO-Y-Z [Y is O, NH, or alkylimino; Z is H, CHL-Ar, alkyl, alkenyl, cycloalkyl, cycloalkenyl or Ar-substituted alkyl or alkenyl, or TCH:C(Q)CH(L)-, where L and Q are H, alkyl or alkenyl; T is Ar or substituted cyclohexyl; Ar is 1- or 2-naphthyl, 2- or 3-furyl, 2-thienyl, 2-, 3- or 4-pyridyl, (un)substituted phenyl; R1 is U, where U is H, (un)substituted alkyl, alkoxy, alkenyl, alkenyloxy, cycloalkyl or cycloalkenyl; X is O or CH-U , provided that if R1 is H, then X is CH-U or if X is O then R1 is U; J is H, alkyl or benzyl; K is alkyl, benzyl or cyclohexylethyl; or J and K may be taken together to form a 5-7 membered heterocyclic ring which may contain O, S, SO or SO2] or their pharmaceutically acceptable salts are claimed. Thus, 3-(3,4,5-trimethoxyphenyl)propyl (2S)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-**pyrrolidinecarboxylate** was prepared by esterification of the acid and showed Ki = 0.025 μM for inhibition of rotamase and ED50 = 80 nM for neurite outgrowth in chick dorsal root ganglion (DRG) cultures.

L2 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2006 ACS on STN
AN 1999:45148 CAPLUS
DN 130:110640
TI Preparation of proline derivatives as inhibitors of rotamase enzyme activity
IN Hamilton, Gregory S.; Steiner, Joseph P.
PA GPI NIL Holdings, Inc., USA
SO U.S., 27 pp., Cont.-in-part of U.S. 5,614,547.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 8

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

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            LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD,
            SE, SG
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            IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN
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    AU 703118           B2   19990318
    GB 2305176          A1   19970402   GB 1996-24257         19960605 <--
    GB 2305176          B2   19991222
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        R:  BE, FR, GR, IE, IT, MC, NL
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    DE 19680256         C2   20030430
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    GB 2324527          A1   19981028   GB 1998-15112         19960605
    GB 2324527          B2   19991222
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    ES 2131457          B1   20000401
    JP 2000503626       T2   20000328   JP 1997-501958        19960605
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        R:  BE, FR, GR, IT, NL, MC, IE
    JP 2000169444       A2   20000620   JP 1999-235727        19960605
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        R:  BE, FR, GR, IT, NL, MC, IE
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    CZ 295106           B6   20050518   CZ 2000-315           19960605
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    TW 453992           B    20010911   TW 1996-85113067      19961024
    ZA 9608984          A    19980625   ZA 1996-8984          19961025
    ZA 9608983          A    19980727   ZA 1996-8983          19961025
    FI 9604328          A    19961230   FI 1996-4328          19961028 <--
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    BG 103977           A    20001130   BG 1999-103977        19971127
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	HK 1022307	A1	20010803	HK 2000-100914	19981222
	AU 9935062	A1	19990819	AU 1999-35062	19990615
	AU 742575	B2	20020110		
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	AU 733685	B2	20010524		
	SE 9903136	A	19990906	SE 1999-3136	19990906
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	DK 9901518	A	19991022	DK 1999-1518	19991022
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	US 2005272780	A1	20051208	US 2005-166220	20050627
PRAI	US 1995-479436	A2	19950607		
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	RU 1997-111860	A3	19960605		
	WO 1996-US9701	W	19960605		
	US 1997-833629	A1	19970408		
	US 2000-605475	A1	20000628		
	US 2002-219887	B3	20020816		

OS MARPAT 130:110640

RE.CNT 76 THERE ARE 76 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI	US 5859031	A	19990112	US 1996-650461	19960521	
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JP 2000503626	T2	20000328	JP 1997-501958	19960605
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EP 992492	A1	20000412	EP 1999-126231	19960605
EP 992492	B1	20040825		
R: BE, FR, GR, IT, NL, MC, IE				
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JP 2000204048	A2	20000725	JP 1999-43437	19960605
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CZ 295106	B6	20050518	CZ 2000-315	19960605
RU 2269514	C2	20060210	RU 2000-115383	19960605
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ZA 9608983	A	19980727	ZA 1996-8983	19961025
FI 9604328	A	19961230	FI 1996-4328	19961028 <--
SE 9604098	A	19961208	SE 1996-4098	19961108 <--
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US 5795908	A	19980818	US 1997-787161	19970123
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HK 1022307	A1	20010803	HK 2000-100914	19981222
AU 9935062	A1	19990819	AU 1999-35062	19990615
AU 742575	B2	20020110		
AU 9935063	A1	19990819	AU 1999-35063	19990615
AU 733685	B2	20010524		
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SE 527193	C2	20060117		
DK 9901518	A	19991022	DK 1999-1518	19991022
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US 6500959	B1	20021231	US 2000-605475	20000628
GR 3035326	T3	20010430	GR 2001-400154	20010131
US 2004049046	A1	20040311	US 2002-219887	20020816
PT 102940	A	20030930	PT 2003-102940	20030414
SE 2004000359	A	20040217	SE 2004-359	20040217
US 2005272780	A1	20051208	US 2005-166220	20050627

AB **Neurotrophic** N-glyoxyl prolyl esters R1COC(:X)-L-Pro-O-Z [R1 = alkyl or alkenyl optionally substituted by cycloalkyl or aryl groups; X = O, S; Z = (un)substituted alkyl or alkenyl], which have an affinity for FKBP-type immunophilins, were prepared for use as inhibitors of the enzyme activity associated with immunophilin proteins, in particular peptidyl-prolyl isomerase (rotamase) enzyme activity. Thus, 3-phenylpropyl (2S)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-**pyrrolidinecarboxylate** was prepared and showed apparent Ki value 42 for inhibition of rotamase activity.

L2 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2006 ACS on STN

AN 1998:599365 CAPLUS
DN 129:198015
TI Rotamase enzyme activity inhibitors
IN Steiner, Joseph P.; Hamilton, Gregory S.
PA GPI Nil Holdings, Inc., USA
SO U.S., 16 pp., Cont.-in-part of U. S. Ser. No. 551,026, abandoned.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 8

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5801197	A	19980901	US 1996-645149	19960513
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	RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN				
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	AU 713302	B2	19991125		
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	CN 1205635	A	19990120	CN 1996-199127	19960826
	JP 11514643	T2	19991214	JP 1996-517308	19960826
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PRAI	US 1995-551026	B2	19951031		
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	WO 1996-US13624	W	19960826		

OS MARPAT 129:198015
RE.CNT 173 THERE ARE 173 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

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PI	US 5801197	A	19980901	US 1996-645149	19960513
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	AU 713302	B2	19991125		
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ST rotamase enzyme inhibitor **pyrrolidinecarboxylate**; **neurotrophic** pipecolic acid deriv

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         67489 CARBOXYLATE
         14733 PRODRUG?
L5          22 (CARBOXYLIC(L)CARBOXYLATE(L)PRODRUG?)

=> s l5 and py<1998
      18297841 PY<1998
L6            7 L5 AND PY<1998

=> d bib hit 1-7

L6   ANSWER 1 OF 7  CAPLUS  COPYRIGHT 2006 ACS on STN
AN   1997:805509  CAPLUS
DN   128:136107
TI   Acyloxymethyl as a drug protecting group: part 4. The hydrolysis of
     tertiary amidomethyl ester prodrugs of carboxylic acid agents
AU   Iley, Jim; Moreira, Rui; Calheiros, Teresa; Mendes, Eduarda
CS   Chemistry Department, The Open University, Milton Keynes, MK7 6AA, UK
SO   Pharmaceutical Research (1997), 14(11), 1634-1639
     CODEN: PHREEB; ISSN: 0724-8741
PB   Plenum Publishing Corp.
DT   Journal
LA   English
RE.CNT  15    THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD
              ALL CITATIONS AVAILABLE IN THE RE FORMAT
SO   Pharmaceutical Research (1997), 14(11), 1634-1639
     CODEN: PHREEB; ISSN: 0724-8741
AB   Novel tertiary amidomethyl esters were synthesized and evaluated as
     potential prodrugs of carboxylic acid agents.
     Hydrolysis of the title compds. in buffer solns. and in plasma were
     studied by UV spectroscopy and HPLC.  Amidomethyl esters were hydrolyzed
     by acid-catalyzed, base-catalyzed and pH-independent pathways.  Both the
     acid-catalyzed, kH+, and pH-independent processes, ko, were strongly
     affected by the electronic and steric nature of the N-substituent in the
     pro-moiety.  For both processes, the electronic effect exerted greater
     influence, and electron-withdrawing substituents retarded reaction.  The
     pH-independent hydrolysis of amidomethyl esters were dependent on the pKa
     of the carboxylate leaving group, giving a Bronsted β1g
     value of -0.91.  The base-catalyzed, kOH-, pathway was mainly affected by
     the steric bulk of the nitrogen substituents in the amide moiety, the
     reactivity being reduced with larger N-substituents.  Hydrolysis in human
     plasma appeared to be mediated by enzymic processes and is dependent upon
     the steric bulk in the carboxylic acid moiety.  Plasma
     hydrolysis rates were inversely dependent on the lipophilicity of the
     ester.  Derivs. containing the Et hippurate carrier are useful
     prodrugs for carboxylic acid-containing drugs with pKa >
     3,5, such as non-steroidal anti-inflammatory agents and valproic acid.

L6   ANSWER 2 OF 7  CAPLUS  COPYRIGHT 2006 ACS on STN
AN   1997:140702  CAPLUS
DN   126:126494
TI   Ortho-Substituted Benzofused Macrocyclic Lactams as Zinc Metalloprotease
     Inhibitors
AU   Ksander, Gary M.; de Jesus, Reynalda; Yuan, Andrew; Ghai, R. D.; Trapani,
     A.; McMartin, Colin; Bohacek, Regine
CS   Res. Dep., Novartis Pharm. Corp., Summit, NJ, 07901, USA
SO   Journal of Medicinal Chemistry (1997), 40(4), 495-505
     CODEN: JMCMAR; ISSN: 0022-2623
PB   American Chemical Society
DT   Journal
LA   English
RE.CNT  34    THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD
              ALL CITATIONS AVAILABLE IN THE RE FORMAT
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SO Journal of Medicinal Chemistry (**1997**), 40(4), 495-505
CODEN: JMCMAR; ISSN: 0022-2623

AB The design and preparation of ortho-substituted benzofused macrocyclic lactams are described. The benzofused macrocyclic lactams were designed as neutral endopeptidase 24.11 (NEP) inhibitors. Docking studies were carried out in a model of thermolysin (TLN) using the MACROMODEL and QXP modeling programs to select suitable ring sizes. These studies predicted that the 11-, 12-, and 13-membered ring macrocyclic lactams would be active in both enzymes TLN and NEP. Good predictability of exptl. results, within this series, of binding to thermolysin and to a lesser extent to NEP was observed A visual comparison, docked at the active site of TLN, is presented for thiorphan, a 10-membered ring macrocycle and an 11-membered ring benzofused macrocyclic lactam. Potent inhibition of both NEP and thermolysin was obtained. The 11-membered ring macrocycle, 2,3,4,5,6,7,8,9-octahydro-2(S)-mercapto-3-oxo-1H-4-benzazacycloundecine-5(S)-**carboxylic** acid, is the most potent inhibitor from this series of compds. (TLN IC50 = 68 nM; NEP IC50 = 0.9 nM). The effects of **prodrug** benzyl 2(R)-[(acetylthio)methyl]-2,3,4,5,6,7,8,9,10,11-decahydro-2-ox-1H-4-benzazacyclotridecine-5(S)-**carboxylate** administered at 10 mg/kg po on plasma atrial natriuretic peptide (ANP) levels in conscious rats was greater than 200% over a 4 h period.

L6 ANSWER 3 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN
AN 1997:21631 CAPLUS
DN 126:69906
TI Angiotensin II-inhibitory action of candesartan cilexetil and its active metabolite, CV-11974, in rabbit aortic strips and conscious rats
AU Shibouta, Yumiko; Inada, Yoshiyuki; Ojima, Mami; Wada, Takeo; Noda, Masakuni; Sanada, Tsukasa; Kubo, Keiji; Kohara, Yasuhisa; Naka, Takehiko; Nishikawa, Kohei
CS Pharmaceutical Res. Div., Takeda Chem. Ind., Ltd., Japan
SO Yakuri to Chiryo (**1996**), 24(10), 2207-2213
CODEN: YACHDS; ISSN: 0386-3603
PB Raifu Saiensu Shuppan K.K.
DT Journal
LA Japanese
SO Yakuri to Chiryo (**1996**), 24(10), 2207-2213
CODEN: YACHDS; ISSN: 0386-3603

AB The angiotensin II (AII) antagonistic action of 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl) biphenyl-4-yl] methyl]-1H-benzimidazole-7-**carboxylic** acid (CV-11974) was examined in an in vitro AII-induced contraction assay using rabbit aortic strips, and that of CV-11974 and its **prodrug**, (±)1-(cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-[[2'(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1H-benzimidazole-7-**carboxylate** (candesartan cilexetil:TCV-116), was examined in an in vivo assay system of AII-induced pressor response in conscious rats. CV-11974 selectively inhibited the AII-induced contraction of rabbit aortic strips in a noncompetitive manner (pD'2:10.08), but at 10 μM it has no effects on the contraction induced by norepinephrine, KCl, serotonin, prostaglandin F2α, or endothelin. EXP3174, a main metabolite of losartan, showed a mixed type of competitive and noncompetitive inhibition with a pD'2 value of 9.06 and a pA2 value of 10.20 for the AII-induced contraction. CV-11974 given i.v. and TCV-116 given orally inhibited the AII-induced pressor response in rats with ID50 values of 0.03 mg/kg and 0.07 mg/kg, resp. These effects of CV-11974 and TCV-116 were approx. 10 times and 40 times more potent than those of EXP3174 and losartan, resp. These results indicate that CV-11947 is a highly potent and selective AII antagonist and TCV-116 has a long-acting AII-inhibitory action in the rat.

L6 ANSWER 4 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN
AN 1996:515414 CAPLUS
DN 125:276411
TI Synthesis and antiviral activity of N-4'-dihydropyridinyl and

dihydroquinolinylcarbonyl-2-hydroxymethyl-5-[cytosin-1'-yl]-1,3-oxathiolane derivatives against human immunodeficiency virus and duck hepatitis B virus

AU Camplo, M.; Charvey-Faury, A. S.; Borel, C.; Turin, F.; Hantz, O.; Traubaud, C.; Niddam, V.; Mourier, N.; Graciet, J. C.; et al.

CS Laboratoire de Chimie Biomoleculaire, Faculte des Sciences de Luminy, Marseille, 13288, Fr.

SO European Journal of Medicinal Chemistry (**1996**), 31(7-8), 539-546
CODEN: EJMCA5; ISSN: 0223-5234

PB Elsevier

DT Journal

LA English

SO European Journal of Medicinal Chemistry (**1996**), 31(7-8), 539-546
CODEN: EJMCA5; ISSN: 0223-5234

AB Dihydropyridine and dihydroquinoline derivs. of 2-hydroxymethyl-5-[cytosin-1'-yl]-1,3-oxathiolane ((±)-3TC) have been prepared The N-4-nicotinate or the N-4-quinoline-**carboxylate** amides were obtained by reacting nicotinic or quinoline-**carboxylic** acids with (±)-3TC in the presence of DCC and HOBT. These derivs. were converted into their corresponding N-methylpyridinium and N-Me quinolinium salts by treatment with MeI in acetone. Reduction of the latter with Na2S2O4 gave dihydropyridine and dihydroquinoline compds. The N-4-trifluorotoluidinonicotinate derivative was obtained from the coupling of niflumic acid and (±)-3TC using BOP and DIEA. The anti-HIV-1-activities of seven derivs. were determined in MT-4 infected cell cultures. Of these compds., the IC50 values ranged from 0.1-100 μM, while the IC50 for (±)-3TC was 0.1 μM. The anti-HBV activities were determined in infected duck hepatocytes. Anti-HBV activities of the (±)-3TC derivs. were half that of the parent drug (±)-3TC. The lipophilicity (partition coeffs.) of these compds. were determined The dihydroquinoline **prodrugs** had greater lipophilicity than the dihydropyridine analogs.

L6 ANSWER 5 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN

AN 1995:521057 CAPLUS

DN 122:281858

TI Effects of TCV-116 and CV-11974 on angiotensin II-induced responses in vascular smooth muscle cells

AU Flesch, Markus; Ko, Yon; Seul, Claudia; Duesing, Rainer; Feltkamp, Heinrich; Vetter, Hans; Sachinidis, Agapios

CS Medizinische Universitaets-Poliklinik, Wilhelmstr. 35-37, Bonn, 53111, Germany

SO European Journal of Pharmacology, Molecular Pharmacology Section (**1995**), 289(2), 399-402
CODEN: EJPPET; ISSN: 0922-4106

PB Elsevier

DT Journal

LA English

SO European Journal of Pharmacology, Molecular Pharmacology Section (**1995**), 289(2), 399-402
CODEN: EJPPET; ISSN: 0922-4106

AB (±)-1-(Cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1H-benzimidazole-7-**carboxylate** (TCV-116, Candesartan) and its active metabolite 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1H-benzimidazole-7-**carboxylic** acid (CV-11974) are specific nonpeptide angiotensin AT1 receptor antagonists. In the present study, the inhibitory potency of these two antagonists on the angiotensin II-induced responses in aortic vascular smooth muscle cells from Wystar Kyoto rats was investigated. The specific binding of 125I-angiotensin II to cells was inhibited by CV-11974 and TCV-116 with a half-maximal inhibitory concentration (IC50) of 3+10-11 M and 1+10-9 M, resp. CV-11974 and TCV-116 inhibited the angiotensin II-induced increase in [3H]thymidine incorporation with an IC50 of 3+10-10 and 5+10-9 M, resp. Both CV-11974 and TCV-116 (10-7

M) completely blocked the angiotensin II-induced increase in c-fos mRNA. The inhibitory potency of the metabolite CV-11974 was about 30-100-fold higher than that of the **prodrug** TCV-116.

L6 ANSWER 6 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN
AN 1993:580705 CAPLUS
DN 119:180705
TI Nonpeptide angiotensin II receptor antagonists. Synthesis and biological activity of potential prodrugs of benzimidazole-7-carboxylic acids
AU Kubo, Keiji; Kohara, Yasuhisa; Yoshimura, Yoshinobu; Inada, Yoshiyuki; Shibouta, Yumiko; Furukawa, Yoshiyasu; Kato, Takeshi; Nishikawa, Kohei; Naka, Takehiko
CS Pharm. Res. Div., Takeda Chem. Ind., Ltd., Osaka, 532, Japan
SO Journal of Medicinal Chemistry (**1993**), 36(16), 2343-9
CODEN: JMCMAR; ISSN: 0022-2623
DT Journal
LA English
SO Journal of Medicinal Chemistry (**1993**), 36(16), 2343-9
CODEN: JMCMAR; ISSN: 0022-2623
AB In order to improve the oral bioavailability (BA) of 2-butyl-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1H-benzimidazole-7-**carboxylic** acid (CV-11194; I; R = Bu)) and 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1H-benzimidazole-7-**carboxylic** acid (CV-11974; I; R = OEt), novel angiotensin II (AII) receptor antagonists, chemical modification to yield **prodrugs** has been examined After selective tritylation of the tetrazole rings in I, treatment of N-tritylated benzimidazole-7-**carboxylic** acids II with a variety of alkyl halides, followed by deprotection with hydrochloric acid, afforded esters of I. Mainly 1-(acyloxy)alkyl esters and 1-[(alkoxycarbonyl)oxy]alkyl esters, double ester derivs., were synthesized. Their inhibitory effect on AII-induced pressor response in rats and oral BA were investigated. (Pivaloyloxy)methyl and (±)-1-[[(cyclohexyloxy)carbonyl]oxy]ethyl esters of I showed marked increases in oral bioavailability which significantly potentiated the inhibitory effect of the parent compds. on AII-induced pressor response. Among them, (±)-1-[[(cyclohexyloxy)carbonyl]oxy]ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1H-benzimidazole-7-**carboxylate** (III, TCV-116) was selected as a candidate for clin. evaluation.

L6 ANSWER 7 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN
AN 1993:573923 CAPLUS
DN 119:173923
TI Pharmacological profile of a highly potent and long-acting angiotensin II receptor antagonist, 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1H-benzimidazole-7-**carboxylic** acid (CV-11974), and its **prodrug**, (±)-1-(cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1H-benzimidazole-7-**carboxylate** (TCV-116)
AU Shibouta, Yumiko; Inada, Yoshiyuki; Ojima, Mami; Wada, Takeo; Noda, Masakuni; Sanada, Tsukasa; Kubo, Keiji; Kohara, Yasuhisa; Naka, Takehiko; Nishikawa, Kohei
CS Pharm. Res. Div., Takeda Chem. Ind., Osaka, Japan
SO Journal of Pharmacology and Experimental Therapeutics (**1993**), 266(1), 114-20
CODEN: JPETAB; ISSN: 0022-3565
DT Journal
LA English
TI Pharmacological profile of a highly potent and long-acting angiotensin II receptor antagonist, 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1H-benzimidazole-7-**carboxylic** acid (CV-11974), and its **prodrug**, (±)-1-(cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1H-benzimidazole-7-**carboxylate** (TCV-116)
SO Journal of Pharmacology and Experimental Therapeutics (**1993**),

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      (FILE 'HOME' ENTERED AT 10:30:26 ON 07 MAR 2006)

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L1            31 S NEUROTROPH?(L)PYRROLIDIN?
L2             4 S L1 AND PY<1998
L3             0 S PYROLIDIN?(L)(CARBOXYLIC(L)CARBOXYLATE(L)PRODRUG?)
L4             0 S NEUROTROPH? AND (CARBOXYLIC(L)CARBOXYLATE(L)PRODRUG?)
L5            22 S (CARBOXYLIC(L)CARBOXYLATE(L)PRODRUG?)
L6             7 S L5 AND PY<1998
L7           ANALYZE L2 4 RN :      26 TERMS

      FILE 'REGISTRY' ENTERED AT 10:40:29 ON 07 MAR 2006
L8            26 S L7
L9             0 S L8 AND PYRROLIDIN?

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                                                   ENTRY    SESSION
FULL ESTIMATED COST                                 5.20      78.64

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                                                   ENTRY    SESSION
CA SUBSCRIBER PRICE                                 0.00      -6.75

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ENTER ANSWER NUMBER OR RANGE (1-):1-3
ENTER DISPLAY CODE (TI) OR ?:rn
L10          ANALYZE L2 1-3 RN :     173 TERMS

=> fil reg
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DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)      SINCE FILE      TOTAL
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CA SUBSCRIBER PRICE                                 0.00      -6.75

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* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added, *
* effective March 20, 2005. A new display format, IDERL, is now *
* available and contains the CA role and document type information. *
* *
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http://www.cas.org/ONLINE/UG/regprops.html

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=> s l10
L11         173 L10

=> s l11 and pyrrolidin?
         548140 PYRROLIDIN?
L12          18 L11 AND PYRROLIDIN?

=> d scan

L12  18 ANSWERS   REGISTRY  COPYRIGHT 2006 ACS on STN
IN   1-Pyrrolidineacetic acid, α-oxo-2-[1-oxo-5-phenyl-2-(3-
     phenylpropyl)pentyl]-, methyl ester, (2S)- (9CI)
MF   C27 H33 N O4
```
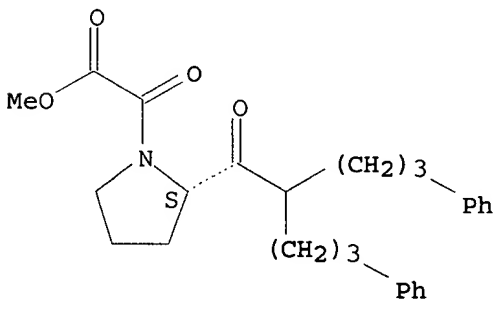

Absolute stereochemistry.

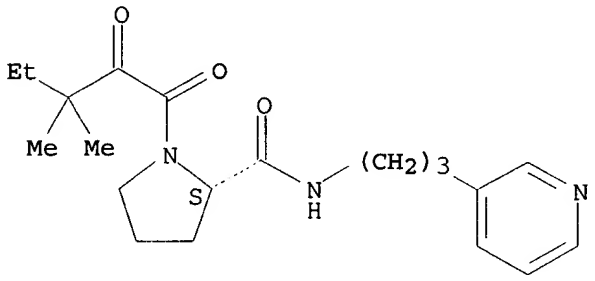


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):17

L12 18 ANSWERS REGISTRY COPYRIGHT 2006 ACS on STN
IN **2-Pyrrolidinecarboxamide, 1-(3,3-dimethyl-1,2-dioxopentyl)-N-[3-(3-pyridinyl)propyl]-, (2S)- (9CI)**
MF C20 H29 N3 O3

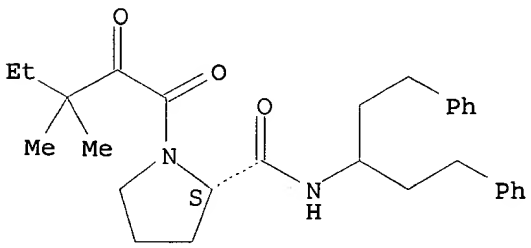
Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L12 18 ANSWERS REGISTRY COPYRIGHT 2006 ACS on STN
IN **2-Pyrrolidinecarboxamide, 1-(3,3-dimethyl-1,2-dioxopentyl)-N-[3-phenyl-1-(2-phenylethyl)propyl]-, (2S)- (9CI)**
MF C29 H38 N2 O3

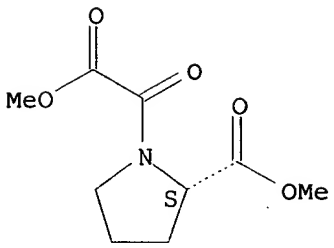
Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L12 18 ANSWERS REGISTRY COPYRIGHT 2006 ACS on STN
IN **1-Pyrrolidineacetic acid, 2-(methoxycarbonyl)-α-oxo-, methyl ester, (2S)- (9CI)**
MF C9 H13 N O5

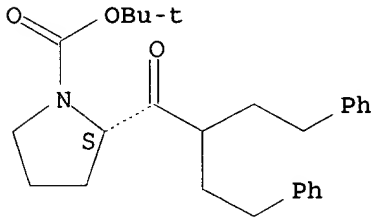
Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L12 18 ANSWERS REGISTRY COPYRIGHT 2006 ACS on STN
IN **1-Pyrrolidinecarboxylic acid, 2-[1-oxo-4-phenyl-2-(2-phenylethyl)butyl]-, 1,1-dimethylethyl ester, (2S)- (9CI)**
MF C27 H35 N O3

Absolute stereochemistry.



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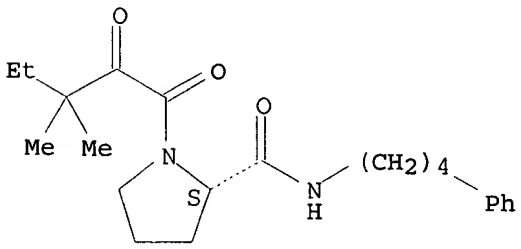
L12 18 ANSWERS REGISTRY COPYRIGHT 2006 ACS on STN
IN **2-Pyrrolidinecarboxamide, 1-(3,3-dimethyl-1,2-dioxopentyl)-N-(4-phenylbutyl)-, (2S)- (9CI)**
MF C22 H32 N2 O3

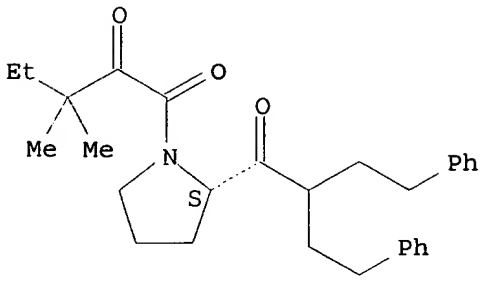
Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L12 18 ANSWERS REGISTRY COPYRIGHT 2006 ACS on STN
IN **Pyrrolidine, 1-(3,3-dimethyl-1,2-dioxopentyl)-2-[1-oxo-4-phenyl-2-(2-phenylethyl)butyl]-, (2S)- (9CI)**
MF C29 H37 N O3

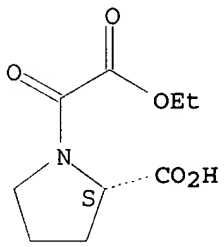
Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L12 18 ANSWERS REGISTRY COPYRIGHT 2006 ACS on STN
IN **1-Pyrrolidineacetic acid, 2-carboxy-α-oxo-, α-ethyl ester, (2S)- (9CI)**
MF C9 H13 N O5
CI COM

Absolute stereochemistry.



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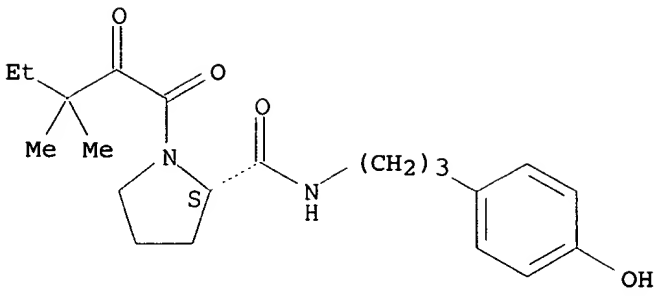
L12 18 ANSWERS REGISTRY COPYRIGHT 2006 ACS on STN
IN **2-Pyrrolidinecarboxamide, 1-(3,3-dimethyl-1,2-dioxopentyl)-N-[3-(4-hydroxyphenyl)propyl]-, (2S)- (9CI)**
MF C21 H30 N2 O4

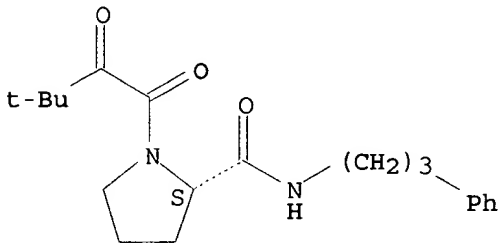
Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L12 18 ANSWERS REGISTRY COPYRIGHT 2006 ACS on STN
IN **2-Pyrrolidinecarboxamide, 1-(3,3-dimethyl-1,2-dioxobutyl)-N-(3-phenylpropyl)-, (2S)- (9CI)**
MF C20 H28 N2 O3

Absolute stereochemistry.



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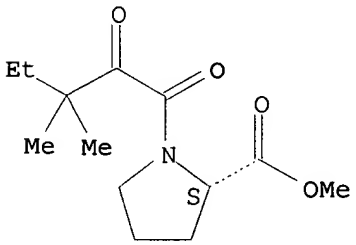
L12 18 ANSWERS REGISTRY COPYRIGHT 2006 ACS on STN
IN L-Proline, 1-(3,3-dimethyl-1,2-dioxopentyl)-, methyl ester (9CI)
MF C13 H21 N O4

Absolute stereochemistry.

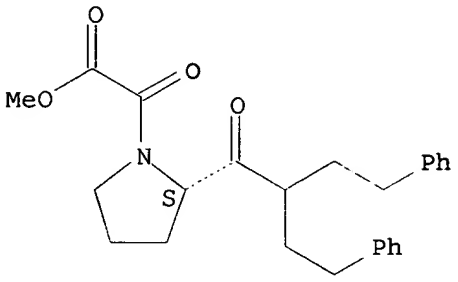


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L12 18 ANSWERS REGISTRY COPYRIGHT 2006 ACS on STN
IN **1-Pyrrolidineacetic acid, α-oxo-2-[1-oxo-4-phenyl-2-(2-phenylethyl)butyl]-, methyl ester, (2S)- (9CI)**

MF C25 H29 N O4

Absolute stereochemistry.



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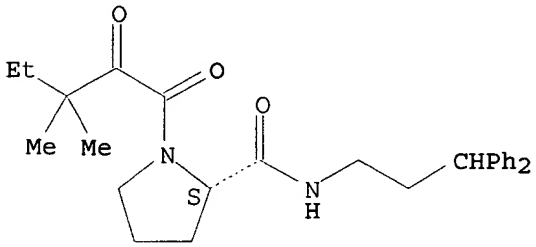
L12 18 ANSWERS REGISTRY COPYRIGHT 2006 ACS on STN
IN **2-Pyrrolidinecarboxamide, 1-(3,3-dimethyl-1,2-dioxopentyl)-N-(3,3-diphenylpropyl)-, (2S)- (9CI)**
MF C27 H34 N2 O3

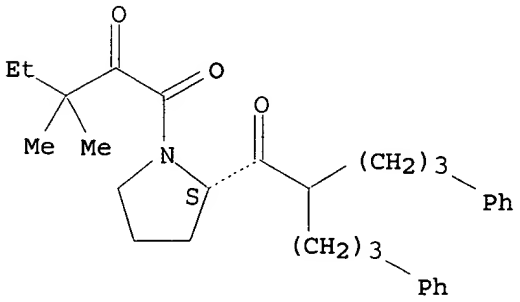
Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L12 18 ANSWERS REGISTRY COPYRIGHT 2006 ACS on STN
IN **Pyrrolidine, 1-(3,3-dimethyl-1,2-dioxopentyl)-2-[1-oxo-5-phenyl-2-(3-phenylpropyl)pentyl]-, (2S)- (9CI)**
MF C31 H41 N O3

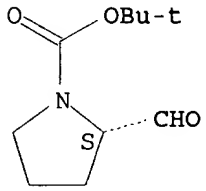
Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L12 18 ANSWERS REGISTRY COPYRIGHT 2006 ACS on STN
IN **1-Pyrrolidinecarboxylic acid, 2-formyl-, 1,1-dimethylethyl ester, (2S)- (9CI)**
MF C10 H17 N O3

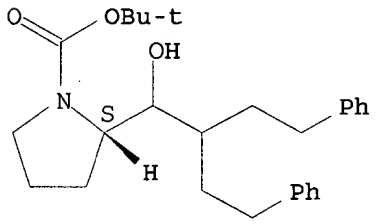
Absolute stereochemistry. Rotation (-).



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L12 18 ANSWERS REGISTRY COPYRIGHT 2006 ACS on STN
IN **1-Pyrrolidinecarboxylic acid, 2-[1-hydroxy-4-phenyl-2-(2-phenylethyl)butyl]-, 1,1-dimethylethyl ester, (2S)- (9CI)**
MF C27 H37 N O3

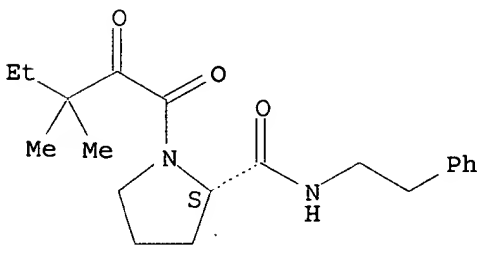
Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L12 18 ANSWERS REGISTRY COPYRIGHT 2006 ACS on STN
IN **2-Pyrrolidinecarboxamide, 1-(3,3-dimethyl-1,2-dioxopentyl)-N-(2-phenylethyl)-, (2S)- (9CI)**
MF C20 H28 N2 O3

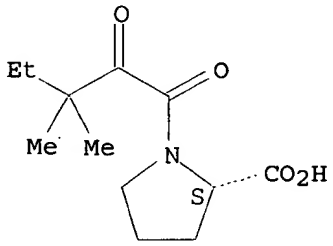
Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L12 18 ANSWERS REGISTRY COPYRIGHT 2006 ACS on STN
IN L-Proline, 1-(3,3-dimethyl-1,2-dioxopentyl)- (9CI)
MF C12 H19 N O4

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

ALL ANSWERS HAVE BEEN SCANNED